REMARKS

In the Office Action dated January 4, 2001, claims 1-8 and 14-17 are under examination. Claims 9-13 and 18-37 are withdrawn from consideration.

In response to the Office Action, Applicants have amended the claims. More specifically, claim 1 as amended is drawn to nucleic acid molecules comprising any one of SEQ ID NOS: 1, 4-5, 7, 9, 11 or 13, or a fragment of any of these SEQ ID NOS wherein the fragment is further delineated as encoding a polypeptide having at least one biological activity of an OGF receptor (OGFr). Support for the amendment of claim 1 is found in the specification, e.g., at page 11, line 28 to page 12, line 7, and page 19, line 9 to page 20, line 5. Claim 3 has been amended to specify the claimed nucleic acid molecule as encoding an OGF receptor and to specify the stringent hybridization conditions. Support for this amendment is found in the specification, e.g., at page 11, line 28 to page 12, line 7 and page 13, line 31 to page 14, line 5. New claims 38-39 have been added and are supported by the specification, particularly at page 12, last paragraph. Claim 5 has been amended to depend from claims 1, 3-4 and 38-39. Claim 14 has been amended to depend from claims 1, 3 and 38-39. Claims 2, 7-13 and 18-37 have been canceled without prejudice. Applicants reserve the right to file one or more continuation and/or divisional application to pursue the subject matter of these canceled claims.

It is respectfully submitted that the foregoing amendment, when considered in view of the following remarks, is deemed to place the application in condition for allowance. Favorable consideration of all pending claims is respectfully requested.

Claims 1-8 and 14-17 are rejected under 35 U.S.C. §101 because the invention is allegedly not supported by a specific, substantial and credibly asserted utility or a well established utility.

The Examiner first alleges that the claims are drawn to nucleic acid molecules coding for a protein (OGF receptor) whose biological function is not disclosed. The Examiner states

that the specification discloses compounds which bind various opioid receptors in tissues containing the receptors of the invention. However, the Examiner contends that the specification does not demonstrate that the receptors of the present application actually bind to an opioid ligand. The Examiner alleges that Applicants' conclusion that the instant receptors are opioid receptors is merely based on tissue localization and homology. While acknowledging the showing in the specification that human OGFr antisense molecules increase cell numbers in culture, the Examiner contends that the instant disclosure has not demonstrated that the effect of the antisense molecules on cell growth is mediated via the claimed receptors. Therefore, the Examiner is of the opinion that no actual and specific biological significance can be attributed to the receptor proteins identified in the specification. The Examiner concludes that, in the absence of knowledge of the natural ligands or biological significance of the instant receptor protein, there is no immediately obvious patentable use for the claimed nucleic acid molecules encoding the protein.

Applicants respectfully submit that the present invention is supported by a specific and substantial utility and a well-established utility. In the first instance, the instantly claimed nucleic acid molecules encode an OGF receptor (or "OGFr"), a splice variant of an OGFr or a fragment of an OGFr. Contrary to the Examiner's allegation, both the ligand of OGFr and at least some of the biological functions of OGFr have been described in the art. As stated in the specification at pages 1-2, the ligand of OGF receptors, OGF (or [Met^5]-enkephalin), is an autocrine produced peptide which is known to be an inhibitory growth factor in development, cellular renewal, cancer, wound healing and angiogenesis. These documented biological functions of OGF are known to be mediated through its receptors (i.e., OGFr). OGFr has also been characterized in the art as sharing certain pharmacological characteristics of classical opioid receptors but distinguished from classical opioid receptors in the binding specificity for OGF and the profile of competitive inhibition by opioid antagonists such as naloxone. See the specification at pages 2-3.

Moreover, the present invention has determined that the isolated nucleic acid molecules encode OGFr, a splice variant of an OGFr or a fragment of an OGFr. Contrary to the Examiner's allegation that the claimed nucleic acid molecules are determined to encode OGFr merely based on tissue localization and homology without any showing of ligand binding, the specification demonstrates that the proteins encoded by the instantly claimed nucleic acid molecules (at least SEQ ID NOS: 1 and 5), after expression and purification from bacterial cells, specifically bind [Met^5]-enkephalin (i.e., OGF) in a manner consistent with receptors for OGF as previously characterized in the art. See page 36-37 (Example 2) and page 42, second paragraph (Example 4) of the specification. The observation that OGFr antisense molecules increase cell numbers in culture is consistent with and provides additional support for the notion that the isolated nucleic acid molecules encode OGFr.

Therefore, it is respectfully submitted that the present specification provides nucleic acid molecules which encode receptor proteins (or variants or fragments thereof) whose ligand and biological functions have been established. The utilities of such nucleic acid molecules are apparent and are asserted in the specification, e.g., the claimed nucleic acid molecules can be used to inhibit undesirable cell growth such as growth of cancerous cells (at page 26 and page 27, lines 24-27); the antisense molecules can be used to promote cell growth when desired (page 27, lines 5-20).

Accordingly, it is respectfully submitted that the specification has asserted at least one specific and substantial utility or one well-established utility. As such, withdrawal of the rejection of claims 1-8 and 14-17 under 35 U.S.C. §101 is respectfully requested.

The specification is objected to and claims 1-8 and 14-17 are rejected under 35 U.S.C. §112, first paragraph. The Examiner states that, since the claimed invention is not supported by a specific, substantial and credible asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention.

As submitted above, the claimed invention is supported by a specific, substantial utility or a well-established utility. The specification clearly teaches one skilled in the art how to use the claimed invention. Thus, the objection to the specification and the rejection of claims 1-8 and 14-17 under 35 U.S.C. §112, first paragraph are overcome. Withdrawal of the objection and the rejection is respectfully requested.

Claims 1-8 and 14-17 are rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled.

The Examiner first alleges that the specification provides no guidance or working examples that the proteins encoded by SEQ ID NO:1, 4, 5, 7, 9, 11 or 13 are opioid growth factor receptors, and that the specification has not provided any binding data using these isolated sequences. The Examiner contends that one skilled in the art would not be able to predict whether these receptors bind opioid ligands (i.e., whether they are in fact opioid growth factor receptors).

Applicants reassert that the claimed isolated nucleic acid molecules encode an OGFr, a splice variant of an OGFr, or a fragment of an OGFr having at least one biological function of the OGFr. Applicants further submit that the specification has demonstrated that the proteins encoded by the instantly claimed nucleic acid molecules, e.g., SEQ ID NOS: 1 and 5, specifically bind [Met^5]-enkephalin (i.e., OGF) in a manner consistent with receptors for OGF as previously characterized in the art. See page 36-37 (Example 2) and page 42, second paragraph (Example 4) of the specification.

The Examiner next alleges that the breadth of claims 1 and 7, reciting "OGFr proteins," and "fragments" of the proteins are overly broad. The Examiner reasons that a "fragment" can be as little as one amino acid, and that the specification provides no guidance or working examples of how to produce a functional fragment, or the function of these fragments.

Applicants respectfully submit that claim 7 has been canceled without prejudice. Claim 1 as amended delineates the fragment as encoding a polypeptide having at least one

biological activity of an OGF receptor (OGFr). As provided in the specification (page 19, lines 9 to 16), the biological activities of an OGFr includes, e.g., binding to Met-enkephalin and inhibition of cell growth. The specification also provides adequate guidance for how to make such a fragment, e.g., page 19, line 17 to page 20, line 5, as well as for how to determine the function of an isolated or modified nucleic acid molecule, e.g., using the binding assays described at page 36-37 and assays at pages 40-41which assess the growth of cultured cells. Thus, it is respectfully submitted that the fragments as recited in the present claims are adequately taught by the present specification.

The Examiner also alleges that the specification does not provide guidance or working examples of the nucleic acid molecules which are "substantially homologous" to (claim 2), or the "complement" of which hybridizes to (claim 3), any one of SEQ ID NO: 1, 4, 5, 7, 9, 11 and 13.

In this regard, Applicants respectfully submit that claim 2 has been canceled without prejudice. Applicants further submit that the nucleic acid molecules of claim 3 as amended encode an OGF receptor and hybridize to specified SEQ ID NOS under the recited stringent conditions. The present specification provides guidance as to how such nucleic acid molecules can be isolated. For example, the specification teaches how SEQ ID NO: 5 (encoding human OGFr) was isolated at pages 42-43 based on hybridization and homology to SEQ ID NO: 1 (rat OGFr). Undeniably, those techniques are readily understood by the skilled artisan.

Regarding claim 4 (drawn to antisense molecules), the Examiner questions the function of the antisense molecules.

Applicants respectfully submit that the specification teaches that the claimed nucleic acid molecules encode an OGFr, a variant or a fragment of an OGFr. As OGFr inhibits cell growth, antisense molecules of an OGFr-encoding gene can be used to antagonize the inhibitory effect of the OGFr on cell growth. In fact, the specification teaches that antisense molecules of

SEQ ID NO: 1 and SEQ ID NO: 5 promote the growth of cells in culture. Thus, the specification provides adequate teaching for the claimed antisense molecules.

Regarding claims 14-17, the Examiner alleges that the specification does not provide any guidance or working examples of any "pharmaceutical composition", or any diseases which can be treated using the claimed nucleic acid molecules, or doses and regimens which would enable those skilled in the art to use the claimed pharmaceutical compositions.

Contrary to the Examiner's allegation, the present specification teaches how pharmaceutical compositions which include any of the claimed nucleic acid molecules are used, as well as the diseases which can be treated by employing such pharmaceutical compositions. For example, at page 27, line 24 to page 28, line 12, the specification teaches that the nucleic acid molecules can be used to treat patients with cancer such as neuroblastoma and gastrointestinal cancers (e.g., colon cancer and pancreatic cancer). As taught in the specification at page 29, lines 28-30, the amount of a nucleic acid to be therapeutically effective can be determined according to the age and the condition of the subject. It is respectfully submitted that those skilled in the art can make such determination without undue experimentation. There is no evidence to the contrary on this record.

In view of the foreging, it is respectfully submitted that the rejection of claims 1-8 and 14-17 under 35 U.S.C. §112, first paragraph, as allegedly not enabled, is overcome. Withdrawal of the rejection is therefore requested.

Claims 1-8 and 14-17 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Examiner indicates that these claims refer to "fragments" of OGFr proteins encoded for by SEQ ID NO: 1, 4, 5, 7, 9, 11 and 13, nucleic acid molecules which are "substantially homologous" to specified SEQ ID NOs, and "antisense" molecules identified by

specified SEQ ID NOs. The Examiner contends that the specification and claims do not provide any guidance as to what changes should be made to obtain the "fragments" and "homologous" sequences. Moreover, the Examiner alleges that the specification fails to describe the common attributes or characteristics that identify members of the genus (i.e., fragments and homologous sequences); and that the disclosure also fails to provide a representative number of species to describe the genus. Thus, the Examiner concludes that Applicants were not in possession of the claimed genus at the time the invention was made.

In response, Applicants submit that the fragment as presently recited in claim 1 encodes a polypeptide having at least one biological activity of an OGF receptor (OGFr) (e.g., binding to Met-enkephalin or inhibition of cell growth). The specification also adequately describes how such a fragment can be made, e.g., page 19, line 17 to page 20, line 5. Thus, it is respectfully submitted that the functional characteristics and the making of the "fragments" as recited in the claim 1 are adequately described in the present specification in compliance with the written description requirement under 35 U.S.C. §112, first paragraph.

Claim 2, drawn to nucleic acid molecules which are "substantially homologous" to specified SEQ ID NOs, has been canceled without prejudice.

New claims 38-39 recite nucleic acid molecules which encode proteins having at least about 75% similarity to specified SEQ ID NOs. Claim 3 recites a nucleic acid molecule which hybridizes to specified SEQ ID NOs. It is respectfully submitted that the specification describes the functional attributes of the claimed nucleic acid molecules, i.e., these molecules encode OGFr proteins. In addition, the specification provides representative species of sequences that bear substantial homology and hybridize to each other, e.g., SEQ ID NO: 5 (encoding human OGFr) and SEQ ID NO: 1 (rat OGFr).

Accordingly, it is respectfully submitted that the claimed nucleic acid molecules, including fragments thereof, sequences hybridizing thereto, sequences encoding proteins homologous to specified SEQ ID NOs, are adequately described in the specification in a manner

that fully complies with the written description requirement of 35 U.S.C. §112, first paragraph. Therefore, the rejection of claims 1-8 and 14-17 under the written description requirement of 35 U.S.C. §112, first paragraph, is overcome. Withdrawal of the rejection is respectfully requested.

Claims 1-8 and 14-17 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite.

The Examiner contends that claims 1-5 and 8 are confusing for reciting "any of SEQ ID NOS". It is suggested that the claims be amended to recite "any one of SEQ ID NOS". Applicants respectfully submit that the claims have been amended to recite "any one of SEQ ID NOS" as the Examiner has suggested.

The Examiner contends that claim 3 and dependent claims 5-6 and 16-17 are vague, as it is allegedly not clear what the metes and bounds of "stringent conditions." Applicants respectfully submit that independent claim 3 has been amended to specify the stringent conditions.

Claim 7 is alleged to be indefinite for the recitation "OGFr." Applicants submit that the rejection of claim 7 is rendered moot in view of the cancellation of claim 7 without prejudice.

In view of the foregoing, it is respectfully submitted that the claims as presently recited are not indefinite. Accordingly, withdrawal of the rejection under 35 U.S.C. §112, second paragraph is respectfully requested.

Claims 1-3, 5, 14 and 16 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Bonaldo et al. The Examiner alleges that Bonaldo et al. teach an isolated nucleic acid molecule which comprises a fragment of SEQ ID NO: 1, which is substantially homologous to SEQ ID NO: 1, and which would hybridize under stringent conditions to SEQ ID NO: 1 (Sequence Comparison A).

Applicants respectfully submit that the rejection of claim 2 under 35 U.S.C. §102(b) is rendered moot in view of the cancellation of claim 2. Applicants further submit that Bonaldo et al. do not teach an isolated nucleic acid molecule which comprises a fragment of SEQ ID NO:

1 wherein the fragment "encodes a polypeptide having at least one biological activity of an OGF receptor (OGFr)" as recited in instant claim 1. Bonaldo et al. do not teach any of the biological activities of an OGF receptor (OGFr). In addition, there is no teaching or evidence that the nucleic acid molecule disclosed by Bonaldo et al. would hybridize to SEQ ID NOS as recited in instant claim 3 under conditions recited in instant claim 3. Nowhere does Bonaldo et al. teach the expression vector of claim 5 or the pharmaceutical compositions of claims 14 and 16. Accordingly, the subject matter of claims 1, 3, 5, 14 and 16 is not taught by Bonaldo et al. Withdrawal of the rejection of claims 1,3,5,14 and 16 as allegedly anticipated by Bonaldo et al. is therefore respectfully requested.

Claims 1, 5-7, 14, 15 and 17 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Pellett et al. The Examiner alleges that Pellet et al. teach an isolated nucleic acid molecule which comprises a fragment of any one of SEQ ID NO.4, 5, 9 and 11 (Sequence Comparisons B-E). The Examiner further alleges that Pellett et al. teach an expression vector, host cell and a method of expressing the fragment.

Applicants respectfully submit that Pellett et al. do not teach an isolated nucleic acid molecule which comprises a fragment of any one of SEQ ID NO.4, 5, 9 and 11 wherein the fragment "encodes a polypeptide having at least one biological activity of an OGF receptor (OGFr) as recited in instant claim 1. Pellett et al. et al. do not teach any of the biological activities of an OGF receptor (OGFr)". Nor do Pellett et al. teach the expression vector of claim 5 or the pharmaceutical compositions of claims 14-15 and 17. Accordingly, the subject matter of claims 1, 5-7, 14-15 and 17 is not taught by Pellett et al. Thus, withdrawal of the rejection of claims 1, 5-7, 14-15 and 17 as allegedly anticipated by Pellett et al. is respectfully requested.

Claims 1, 5, 14 and 16 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Fliegel et al. The Examiner alleges that Fliegel et al. teach an isolated nucleic acid molecule comprising a fragment of SEQ ID NO: 7 as well as an expression vector comprising such nucleic acid molecule.

Applicants respectfully submit that Fliegel et al. do not teach an isolated nucleic acid molecule which comprises a fragment of SEQ ID NO: 7 wherein the fragment "encodes a polypeptide having at least one biological activity of an OGF receptor (OGFr)" as recited in instant claim 1. Fliegel et al. do not teach any of the biological activities of an OGF receptor (OGFr). Nor do Fliegel et al. teach an expression vector comprising a fragment of SEQ ID NO: 7 which "encodes a polypeptide having at least one biological activity of an OGF receptor (OGFr)". Accordingly, claims 1, 5, 14 and 16 are not anticipated by Fliegel et al. Withdrawal of the rejection of claims 1, 5, 14 and 16 under 35 U.S.C. §102(b) as allegedly anticipated by Fliegel et al. is respectfully requested.

Claims 1, 5, 14 and 16 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Everett et al. The Examiner alleges that Everett et al. teach an isolated nucleic acid molecule comprising a fragment of SEQ ID NO: 13 (Sequence Comparisons G).

Applicants respectfully submit that Everett et al. do not teach an isolated nucleic acid molecule which comprises a fragment of SEQ ID NO: 13 wherein the fragment "encodes a polypeptide having at least one biological activity of an OGF receptor (OGFr)" as recited in instant claim 1. Everett et al. do not teach any of the biological activities of an OGF receptor (OGFr). Nor do Everett et al. teach an expression vector comprising a fragment of SEQ ID NO: 13 which "encodes a polypeptide having at least one biological activity of an OGF receptor (OGFr)". Accordingly, claims 1, 5, 14 and 16 are not anticipated by Everett et al. Withdrawal of the rejection of claims 1, 5, 14 and 16 under 35 U.S.C. §102(b) as allegedly anticipated by Everett et al. is respectfully requested.

Claims 1, 5-7 and 14-17 are rejected under 35 U.S.C. §102(e) as allegedly unpatentable by Chambon et al. (U.S. Patent No. 5,861,381). The Examiner alleges that Chambon et al. teach a fragment of SEQ ID NOs: 5, 9, 11 as well as a vector, host cell and method of making proteins encoded by these fragments.

Applicants respectfully submit that Chambon et al. do not teach an isolated nucleic acid molecule which comprises a fragment of SEQ ID NO: 13 wherein the fragment "encodes a polypeptide having at least one biological activity of an OGF receptor (OGFr)" as recited in instant claim 1. Chambon et al. do not teach any of the biological activities of an OGF receptor (OGFr). Nor do Chambon et al. teach an expression vector comprising a fragment of SEQ ID NO: 13 which "encodes a polypeptide having at least one biological activity of an OGF receptor (OGFr)". Accordingly, claims 1, 5, 14 and 16 are not anticipated by Chambon et al. Withdrawal of the rejection of claims 1, 5, 14 and 16 under 35 U.S.C. §102(b) as allegedly anticipated by Chambon et al. is respectfully requested.

Claims 6 and 7 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over the three primary references Bonaldo et al., Fliegel et al., or Everett et al. each in view of Chambon et al. (U.S. Patent No. 5,861,381). Bonaldo et al., Fliegel et al. and Everett et al. teach an isolated nucleic acid molecule comprising a fragment of SEQ ID NOs: 1, 7 or 13, respectively and an expression vector as discussed in the above rejections under 35 U.S.C. §102(b). The Examiner admits that neither Bonaldo et al., nor Fliegel et al., nor Everett et al. teach a cell transformed with an expression vector, or a method of producing a fragment of an OGFr protein. However, the Examiner contends that Chambon et al. teach a cell transformed with an expression vector, as well as a method of producing a fragment of a protein. The Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the invention of Chambon et al. by substituting the cDNA in the polycloning region of the vector with the polynucleotide (cDNA) of either Bonaldo et al., Fliegel et al. or Everett et al. for the purpose of transfecting a host cell and, therefore, producing a protein of interest.

Applicants respectfully submit that none of Bonaldo et al., Fliegel et al., or Everett et al. teach an isolated nucleic acid molecule which comprises a fragment of specified SEQ ID NOS wherein the fragment "encodes a polypeptide having at least one biological activity of an

OGF receptor (OGFr)". None of these references teach any of the biological activities of an OGF receptor (OGFr). Such deficiencies of the primary references are not cured by the secondary reference to Chambon et al. Thus, the cited references taken together do not suggest to those skilled in the art to make an isolated nucleic acid molecule which comprises a fragment of specified SEQ ID NOS wherein the fragment "encodes a polypeptide having at least one biological activity of an OGF receptor (OGFr)". As such, the rejection of Claims 6 and 7 under 35 U.S.C. §103(a) based on Bonaldo et al., Fliegel et al., or Everett et al. each in view of Chambon et al. is overcome. Withdrawal of the rejection is respectfully requested.

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

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Encl.: Version with Markings to Show Changes Made

Version with Markings to Show Changes Made

Claims 2, 7-13 and 18-37 have been canceled.

Claims 1, 3-5, 14 have been amended as follows:

1. (Amended) An isolated nucleic acid molecule comprising any one of SEQ ID NOs: 1, 4-5, 7, 9, 11 or 13, or a fragment [thereof] of any one of SEQ ID NOs: 1, 4-5, 7, 9, 11 or 13, wherein said fragment encodes a polypeptide having at least one biological activity of an OGF receptor (OGFr).

3. (Amended) An isolated nucleic acid molecule, the complement sequence of which [hybridize] hybridizes under stringent conditions to any of SEQ ID NOs: 1, 4-5, 7, 9, 11 and 13, wherein said nucleic acid molecule encodes an OGFr, and wherein said stringent conditions comprise hybridization at about 65°X and washing in about 0.1X-2x SSC with about 0.1% SDS.

4. (Amended) An isolated nucleic acid molecule comprising an antisense sequence of any one of SEQ ID NOs: 1, 4-5, 7, 9, 11 [and] or 13.

5. (Amended) An expression vector comprising any one of the isolated nucleic acid molecules of claims [1-4] 1, 3-4 or 38-39.

14. (Amended) A pharmaceutical composition comprising the isolated nucleic acid molecule of [claim] any one of claims 1, 3 or 38-39 and a pharmaceutically acceptable carrier.

Claims 38-39 have been added:

38. An isolated nucleic acid molecule encoding a protein wherein said protein has a sequence as set forth in any one of SEQ ID NOS: 2, 6, 8, 10, 12 or 14.

39. An isolated nucleic acid molecule encoding a protein wherein said protein is an OGF receptor and has a sequence which bears at least about 75% similarity to any one of SEQ ID NOS: 2, 6, 8, 10, 12 or 14.